Department of Veterans Affairs Pharmacy Benefits Management Service and Medical Advisory Panel

Primary Care Outpatient Algorithm: Treatment of Acute Insomnia (Short-term, 1-4 weeks) and Chronic Insomnia (Long–term, > 1 month)

Assessment/evaluation of other **co-morbid conditions** that is known to interfere with sleep should be performed and documented. Drug use, withdrawal, or the attempt to adjust any **medications/substances** that could interfere with sleep should be documented.

An adequate **sleep history interview** should be performed. Provide patient with a **sleep diary** with instructions. Document the **type of insomnia disorder** at each visit.

Instruct patient on the **basic principles of sleep hygiene.**

If patient has primary insomnia (i.e., insomnia does not occur exclusively during the course of another sleep or mental disorder and is not due to the direct physiological effects of a substance or a general medical condition) evaluate and document any improvement in sleep. Enforce good sleep-hygiene interventions at each visit. Consider providing (if available and feasible) supportive psychotherapy including **other types of cognitive behavioral therapy** if needed.

Available Medications on VA Formulary for *Acute* Insomnia

- **Non-Benzodiazepine Receptor Agonist**

Short trial of zolpidem IR:
Women: 5 mg at bedtime x 7-10 days with no refills
Men: 5-10 mg at bedtime X 7-10 days with no refills

- **Benzodiazepine**

Short trial of temazepam 7.5-30 mg at bedtime x 7-10 days with no refills.

- **Sedating Antidepressant**

Trazodone†* 25-50 mg at bedtime x 2 weeks with no refills.

(*2 wk study was performed in pts with chronic insomnia)
(† off-label use)

Available Medications on VA Formulary for *Chronic* Insomnia

- **Non-Benzodiazepine Receptor Agonist**

Zolpidem IR:
Women: 5 mg at bedtime x 2 refills
Men: 5-10 mg at bedtime x 2 refills

- Consider minimizing the dosing frequency* (e.g., take no fewer than 3 and no more than 5 tablets per week. (3-5x/week x QTY #20/month with 2 refills).
- For both men and women, the 5 mg dose could be increased to 10mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness.

- **Benzodiazepine**

Temazepam† 7.5mg-30mg at bedtime x 2 refills.

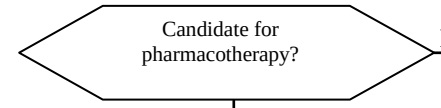
- Consider minimizing the dosing frequency despite lack of data.

- **Sedating Antidepressant**

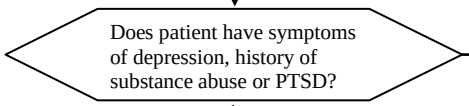
Trazodone† 25-100 mg (titrated) at bedtime x 2 refills if patient has concurrent depression or PTSD.

Doxepin†***** 25-50mg at bedtime x 4 weeks
* In studies, this dosing was utilized in patients with primary insomnia (i.e. insomnia does not occur exclusively during the course of another sleep or mental disorder and is not due to the direct physiological effects of a substance or a general medical condition). It should be noted that doxepin is considered inappropriate for use in older patients because of its high anticholinergic adverse effects.

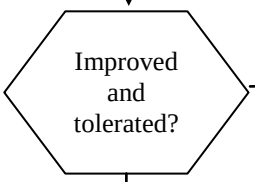
(† off-label use)

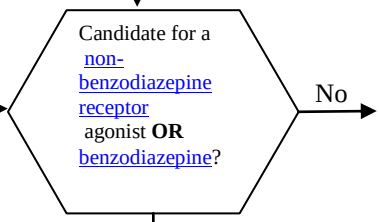


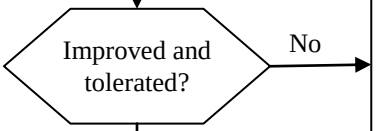
Review **co-morbid conditions** before choosing specific therapy. Educate patient on the use, duration of therapy, possible ADRs of medications.



Consider a sedating antidepressant as an alternative.







Document improvement. Continue to monitor and review/enforce good sleep hygiene interventions with patient and/or caregiver/spouse at each clinic visit.

Review adherence to adjunctive behavioral modification therapy and basic sleep interventions. Review again **basic sleep hygiene** education and interventions with patient. Consider instructing patient on **other types of cognitive behavioral therapy.** Re-evaluate the presence/change of any co-morbid conditions or **medication/ substances.**

Consultation with a sleep disorders specialist (e.g., neurologists, pulmonologists, psychiatrists, medical practitioners board certified in sleep medicine) or a behavioral therapist that is experienced in sleep intervention techniques may be necessary if the standard behavioral treatments are not effective and the patient is not a candidate for pharmacologic treatment or the pharmacologic agent is not continued.

For additional information on Department of Veterans Affairs Pharmacy Benefits Management Service and Medical Advisory Panel, see attached Guidance for Treatment of Insomnia in Veterans in the Primary Care Setting.

Department of Veterans Affairs Pharmacy Benefits Management Service and Medical Advisory Panel
Guidance for Treatment of Insomnia in Veterans in the Primary Care Setting
March, 2013

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

An insufficient number of controlled studies, lack of comparative studies, and inconsistent reporting of meaningful outcome measures make the development of evidence-based guidelines for the treatment of primary insomnia in the Veteran population difficult. It is recognized that in primary care, screening for sleep problems is often overlooked or perhaps, not even performed. Screening entails taking an adequate sleep history including sleep and wakefulness patterns, history from the bed partner, family history of sleep disorders, and previous treatments. To aid the provider in the management of this condition, the patient and/or caretaker(s) needs to be trained to appropriately use monitoring tools such as sleep diaries.

On January 10, 2013, the U.S. Food and Drug Administration (FDA) recommended lowering the bedtime doses of immediate and extended-release zolpidem products because new data show that increased blood levels in some patients may exist the morning after use and impair activities that require alertness, including driving, despite feeling fully awake. Women are more susceptible to next-morning impairment due to a slower rate of elimination of zolpidem than men. For more details, see http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm and http://www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf.

Therefore, the purpose of this document is two-fold. First, it is to promote and improve screening of sleep problems in the Veteran population. The second purpose of this document is to provide guidance to practitioners in the clinical decision-making, to standardize and improve treatment of insomnia in Veterans, and to promote cost-effective drug prescribing.

Background: The prevalence of insomnia reported in the literature is difficult to determine due to the lack of standardized diagnostic and screening methods, including variable assessment methods used to evaluate its presence and clinical significance as well as an inconsistent operational definition of insomnia used amongst the clinical studies. In the literature, insomnia has been classified as "short-term," "transient," "occasional or intermittent," "chronic," and "day-time functional impairment."

It has been reported that 50% of primary care patients experience insomnia, only 1/3 actually mention the problem and 5% actually seek treatment. (Ancoli-Israel S et al. 1999; Smith MT et al. 2002; Shochat T et al. 1999) Most experts agree that the prevalence of insomnia is more common in women, older adults particularly those with depression, and patients with chronic medical or psychiatric problems. The prevalence rates of insomnia in adults aged 65 and over have been reported to be between 12 and 40%. (Morin C. 1999). It is not well-known how to best manage insomnia in specific sub-populations. However, it is known that there are consequences of not treating insomnia including a higher risk of depression, cognitive impairment, mood disturbances, decrease job performance, increase daytime fatigue, and a frequent use of medical services contributing to increase in healthcare costs. Previously, it was believed insomnia was the result of a co-existing secondary condition(s) or medication(s) and would improve if the underlying disorder(s) was treated or the agent(s) causing insomnia was removed. However, new evidence suggests that insomnia can be an independent disorder and can continue to exist despite successful treatment of the secondary condition and/or removal of medication that may interfere with sleep. Despite that new evidence, an assessment/evaluation of the co-morbid conditions associated with sleep disturbances should still be performed and documented. Drug use, withdrawal, or the attempt to adjust any medications/substances that could interfere with sleep should also be documented.

ACUTE INSOMNIA: (less than one month in duration) The management of acute insomnia has traditionally involved pharmacotherapy, although no ideal hypnotic agent is available. Although the choice of a drug is primarily determined by clinical efficacy, the risk of accidents, hip fractures and falls due to residual effects should be taken into consideration in selecting a sedative hypnotic agent. Selection of the safest drug and dose possible among those available is a first step towards minimizing the risk. A second step is to adequately inform patients about any risks and ways to minimize them by adjusting their behavior. As a result, emphasizing nonpharmacologic approaches alone or in combination with short-term pharmacologic treatment versus indefinite pharmacologic treatment must be in the forethought of a provider when an appropriate treatment plan for acute insomnia is being discussed. Initially, if a patient has an inadequate response to simple basic-sleep hygiene principles, additional nonpharamcologic approaches (e.g. relaxation, cognitive/behavioral therapy) in combination with a pharmacologic agent short-term is an appropriate approach for acute insomnia. Thus, the goals of treatment for acute insomnia which should be discussed with the patient is to reverse the sleep disruption and accompanying deterioration of daytime performance, as well as to prevent possible evolution to chronic insomnia.

CHRONIC PRIMARY INSOMNIA: The evidence for management of chronic insomnia with pharmacotherapy has not been systematically evaluated. As a result, difficulty arises in attempting to provide guidance on the optimal duration of therapy for primary chronic insomnia let alone those with chronic medical and psychiatric co-morbid conditions. Literature reveals that the lack

of knowledge about non-drug treatment and limited access to other forms of professional help were the main reason for prescribing sleeping pills. (Baillargeon L et al. 1996). Two early NIH consensus conferences (1983, 1990) concluded that long-term use of hypnotic medications remains controversial because of the potential risk of tolerance and dependency. More recently, evidence suggests that relaxation and cognitive/behavioral therapy are effective in the management of chronic insomnia in subsets of population. (AHRQ Publication No. 05-E021-2, June 2005)

Currently, published data of one-year in duration with the newer sedative hypnotics exists. Again, it needs to be reinforced that no ideal hypnotic agent is available. When pharmacologic treatment is prescribed, patients should be adequately informed of the duration and severity of residual effects of the hypnotic agent. Residual effects depend on the dose administered; start with the lowest dose possible, particularly in the elderly. Reports of daytime residual effects of these types of drugs are more likely to be affected by older individuals, as well as increasing the risk for falls and fractures. Do not double the dose without consideration of the consequences of residual effects. These agents should be avoided when next day's activities involves skilled work and where impairment of performance could be a danger to themselves or others. If a sedative hypnotic agent that is likely to produce moderate or severe effects cannot be avoided, the recommendation to prohibit driving completely at the start of treatment should be considered. Advise patients not to drive when they feel sleepy, dizzy or are experiencing a lack of concentration. However, it should also be made clear to them that the absence of such feelings does not mean their performance is normal. The use of sedative hypnotic agents in combination with other psychoactive drugs largely increases the risk of residual effects, and should be avoided if all possible.

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Antidepressants: Trazodone/Doxepin

Trazodone has been prescribed for chronic insomnia despite the lack of good evidence. A two week trial, rated fair-quality by the Oregon Evidence-based Practice Center assessed the use of short term zolpidem, trazodone and placebo in patients with primary insomnia. Sleep latency was shorter with zolpidem after 1 week (assessed by questionnaire), compared to trazodone but the difference was not significant at week 2. Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2. More patients reported daytime somnolence with trazodone. Withdrawals due to adverse events and overall adverse events were similar between the drugs.

In a double-blind, randomized, placebo-controlled trial, doxepin 25-50mg was studied objectively in 47 drug-free patients with primary insomnia over a 4 week period followed by 2 weeks of placebo withdrawal. Doxepin significantly increased sleep efficiency compared with patients whom received placebo. Latency to sleep onset was not affected; however the patients had normal baseline sleep latencies. Patients perceived that doxepin caused significantly better global improvement at the first day of treatment. Patients rated sleep quality and working ability to be significantly improved with doxepin during the whole treatment period. Patients with severe rebound insomnia occurred more frequently in the doxepin group compared to placebo.

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Antihistamine: Diphenhydramine

Diphenhydramine for the treatment of insomnia is not supported by rigorous data. In a double-blind, randomized, cross-over trial in 15 healthy men, aged 18-50, diphenhydramine 50 mg twice a day demonstrated significant impairment of performance. Tolerance was noted within 3 days of administration. In 144 psychiatric patients with insomnia, the hypnotic effect of diphenhydramine 12.5-50 mg for 2 weeks was significantly greater in those patients who had not been treated previously with the medication. In another double-blind, randomized, placebo-controlled, cross-over study with diphenhydramine 50-75mg, temazepam (15 and 30mg) and valerian in 14 healthy elderly volunteers (mean age, 71.6); temazepam 30mg and both doses of diphenhydramine elicited significantly greater sedation than placebo, $p<0.5$, all). No difference in sedation scores were noted between 50 and 75 mg diphenhydramine. No psychomotor impairment was detected with diphenhydramine 50 mg. However, in another study using a driving simulator, diphenhydramine 50 mg did impair the driving performance to a greater extent than alcohol.

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Prepared November 2007, Updated March 2013. Contact person: Janet H. Dailey, PharmD, VA Pharmacy Benefits Management Services.

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Benzodiazepines:

Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. Evidence Report/Technology Assessment No. 125. June 2005.
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Holbrook AM, Crowther R, Lotter A, et al. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ 2000; 225-33.
Nowell PD, Mazumar S, Buysee D, et al. Benzodiazepines and zolpidem for chronic insomnia: A meta-analysis of treatment efficacy. JAMA 1997; 278:2170-77.

Newer Sedative Hypnotics:

Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. Evidence Report/Technology Assessment No. 125. June 2005.
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Miscellaneous Agents

Atypical Antidepressants/Quetiapine:

Fifteen subjects with refractory post-traumatic stress disorder (PTSD) (combat and noncombat trauma) were enrolled in an 8-week open-label trial for PTSD in which quetiapine was added to a selective serotonin reuptake inhibitor (SSRI). The mean dose prescribed in the study was 216mg per day. The addition of quetiapine proved significant relief from PTSD symptoms with a 42% overall improvement in PTSD symptoms based on the Clinician-Administered PTSD Scale (CAPS). Sleep measures as a secondary measure was evaluated using the Pittsburgh Sleep Quality Index (PSQI). The score from the PSQI improved by approximately 42% compared to baseline scores, (p=0.004).

In an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, quetiapine monotherapy (300 or 600mg/day) in comparison with placebo on overall quality-of-life (QOL) and quality of sleep in adults with bipolar I or II depression was evaluated. Patients were adult outpatients, aged 18-65 years and were in a current episode of depression with a duration of greater than 4 weeks but less than 1 year. Quetiapine was initiated at 50mg/day and administered to achieve a target daily dose of 300mg/day by day 4, or 600mg/day by week 1. Zolpidem (5-10mg/day at bedtime for insomnia) and lorazepam (1-3mg/day for severe anxiety) during the first 3 weeks of treatment were permitted. Both doses of quetiapine significantly improved QOL over baseline values in comparison with placebo. As a secondary outcome, quetiapine therapy also caused a significant improvement in quality of sleep compared with placebo measured using the Pittsburgh Sleep Quality Index (PSQI).

Ahearn EP, Mussey M, Johnson C, et al. Quetiapine as an adjunctive treatment for post-traumatic stress disorder: an 8-seek open-label study. Int Clin Psychopharmacol 2005; 21:29-33.
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Prazosin:

Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003; 160: 371-73.
Taylor F, and Raskind MA. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. J Clin Psychopharmacol 2002; 22: 82-5.

Zolpidem-Intermittent Dosing:

Cluydts R, Peeters K, DeBouyalisky I, et al. Comparison of continuous vs. Intermittent administration of zolpidem in chronic insomniacs: a double-blind, randomized, pilot study. J Int Med Res. 1998; 26:13-24.
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* Applicable agents currently available on the VA National Formulary as of 5-2007

Prepared November 2007, Updated March 2013. Contact person: Janet H. Dailey, PharmD, VA Pharmacy Benefits Management Services.

Appendix: Additional Information/Resources Regarding Management of Insomnia

Table 1: Sleep History Interview **[Click here to return to algorithm]**

Questions To Ask Patients/Caregivers When Obtaining a Basic Sleep History (involving the usual sleep period)

1. What time do you go to bed?
2. What time do you wake up in the morning?
3. Would you say you get ___ hours (based on answers from questions 1 and 2) of sleep every night?
4. When you do go to bed, how long does it take for you to get to asleep?
    - What keeps you awake?
5. Do you sleep through the night?
    - If not, how many times do you wake up, and why?
    - When you do fall back to sleep, how long does it take you to get back to sleep?
6. What time do you get out of bed for the day?
7. How do you feel when you wake up in the morning?
8. How long does it take you to "get going" in the morning?
9. Do you believe your ability to perform daytime activities has been affected by your trouble sleeping?
10. Do you try to sleep longer on weekends or days off? If so, how much?
11. Do you smoke?
    - If so, how much?
    - Do you smoke in the evening?
12. Do you drink alcohol in the evening?
    - Do you drink alcohol to help you fall asleep?

Questions to Ask Patients/Caregivers about behaviors that affect sleep: (rule-out other sleep disorders)

1. Do you nap during the day, when, and for how long? (hypersomnia)
2. Do you snore? Does the bed partner observe episodes of where you stop breathing? (obstructive sleep apnea)
3. When you are in bed, do you have an irresistible urge to move your legs? (restless leg syndrome)
    - Does your bed partner report that you kick or jerk your legs frequently during the night?
4. Do you eat at night?
5. Do you take any medications or over-the-counter preparations, herbal remedies, or psychoactive substances to assist with sleep?
6. Where do you sleep, and what surrounds you in your place of sleep, e.g. computer, television, paperwork, room lighting, and outside noise?
7. Do you drink coffee, tea, chocolate and caffeinated colas? How much?
8. How has your mood been recently? Are you still able to enjoy social/family activities? (depression)
9. Have you been told that you act strangely during your sleep? (parasomnias)

Adapted from Wilson S. and Nutt D. Prescriber 2005; 19:29-41. Wolkove N. et al. CMAJ 2007; 176:1449-454.

There is a variety of co-morbid conditions associated with insomnia. Table 2 indicates some medical, psychiatric, and environmental disorders known to interfere with sleep. A work-up for insomnia would include the assessment and evaluation of these conditions.

Table 2: Co-morbid conditions that interfere with sleep* **[click here to return to algorithm]**

Medical			
Angina	CHF	Hyperthyroidism	PUD
Arthritis	Crohn's disease	Hypoglycemia	Periodic limb movements
Asthma	Cushing's disease	Malignancy	Renal insufficiency
Bronchitis	Cystic fibrosis	Migraine	Restless legs syndrome
Carpal tunnel syndrome	Emphysema	Nocturia	Rheumatoid Arthritis
Chronic bladder infection	Epilepsy	Obstructive uropathy	Sleep apnea
COPD	Fibromyalgia	Paresthesias	Stroke
Chronic painful physical conditions (CPPC)	Gastroesophageal reflux	Parkinson's disease	
Psychiatric and/or Psychological			
Acute stress disorder	Dementia	Posttraumatic stress disorder	
Alcohol or substance abuse	Dysthymic disorder	Separation anxiety disorder	
Anxiety disorders	Major depressive episode	Somatoform disorders	
Bipolar disorder			
Environmental			
Shift work			

*Please note: Extent to which treatment for these conditions ameliorates insomnia remains unclear. Often, treatment of insomnia in addition to treating the co-morbid condition may need to occur concurrently

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Table 3 list medications/substances which could interfere with sleep or associated with daytime somnolence. Documentation of drug use, withdrawal, or the attempt to adjust any medication/substances that could interfere with sleep should be documented.

Table 3: Medications/Substances which could interfere with sleep or daytime somnolence **[click here to return to algorithm]**

Alcohol	Beta-2 Agonist	Statins
Anticonvulsants	Caffeine (over-the-counter products)	Nicotine
Analgesics (e.g., narcotics)*	Clonidine	Methyldopa
Anticholinesterase inhibitors (e.g., donepezil)	CNS Stimulants	Opioids Resperine
Antidepressants (e.g. MAOIs, occasionally SSRIs)	Decongestants (e.g. pseudoephedrine)	Quinidine
Antidepressants (e.g, imipramine, trazodone)*	Diet pills	Selective serotonin reuptake inhibitors
Antihistamines*	Diuretics	Steroids
Antihypertensives (e.g., clonidine)*	Herbal preparations containing M Huang	Stimulants
Antineoplastics	Histamine 2-Blockers (e.g., cimetidine)	Theophylline
Beta-blockers (propranolol, atenolol, pindolol)	Hormones	

*associated with daytime sleepiness

Table 4: Insomnia Educational Tools and Resources **[click here to return to algorithm]**

Patient Resources for Basic Sleep Hygiene Instructions and Education	***http://www.nhlbi.nih.gov/health/health-topics/topics/inso/*** ***http://www.sleepfoundation.org/article/sleep-topics/healthy-sleep-tipsq*** ***http://nihseniorhealth.gov/sleepandaging/insomnia/01.html***
Example of sleep diary	http://sleep.buffalo.edu/sleepdiary.pdf.
Professional Education	***http://www.sleepfoundation.org*** http://sleepdisorders.sleepfoundation.org/

Table 5: Definitions of Insomnia-Related Effectiveness Outcomes

Sleep Effectiveness Outcomes	Definitions
Sleep latency	Time period that it takes for a person to fall asleep
Sleep duration	Time period a person remains asleep
# awakenings	Number of times patient wakes up
WASO-(wake time after sleep onset)	Total time that a person is awake between sleep onset and final wake-up
Sleep quality	Usually measure by patient questionnaire (Likert or visual analogues)
Daytime alertness	Measured by patient self-report
Rebound insomnia	Worsening of insomnia from baseline (prior to pharmacotherapy) upon treatment discontinuation
Sleep Efficiency	Reported time asleep divided by the reported time in bed.

Table 6: Sleep Hygiene Education* **[click here to return to algorithm]**

Sleep hygiene education is useful for all patients regardless of diagnosis. It ensures that patient's behaviors and lifestyle are optimized to improve sleep efficiency
by educating patients about the interaction between lifestyle, environment, and sleep physiology.

- Avoid or limit caffeinated containing products, nicotine, and alcohol especially later in the day.
- Avoid drinking excess liquids after supper to avoid having to get up during the night to go to the bathroom.
- Avoid or limit daytime naps to 30 minutes in the early afternoon before 3:00 pm.
- Go to bed only when sleepy. Sleep only as much as needed to feel refreshed. Staying in bed longer can result in fragmented/shallow sleep on following nights.
- Create a dark, quiet, temperature-controlled bedroom. (e.g., change the number of blankets you use; use earplugs; close the door if noisy)
- Avoid heavy meals within 2 hours of bedtime; a light snack might help if hungry.
- Maintain a regular daily schedule of activities including bedtime and awakening times, 7 days/week. Use an alarm clock if needed.
- Exercise regularly during the daytime, preferably 4-5 hours before bedtime.
- Use the bed and bedroom only for sleeping or sexual activity. Do not eat, work or watch television while in bed.
    - If you can not sleep, if possible, get out of bed and go to another room if you have not fallen asleep within 15-20 minutes. Go to another room, read or engage in other quiet activities; or do other relaxation activities before attempting to sleep again. Return to bed only when sleepy. Repeat if necessary. Do not watch the clock; turn the clock around or cover it up.
- Solve problems before retiring. If not possible, write down your worries, plans and strategies during the early evening and not at bedtime.
- Correct extrinsic factors such as environmental disruption (e.g., pets or snoring partner)
- Establish a "wind-down" routine going to bed and develop and maintain bedtime "rituals" that make going to sleep a familiar routine; for example:
    - Setting time to relax before bed with 20-30 minutes of relaxation (e.g. soft music, medication, breathing exercises
    - Take a warm bath
    - Have a light snack, which could include: warm milk, foods high in tryptophan, such as bananas, carbohydrates, which can help induce sleep

Adapted from Petit L, et al. Age Ageing 2003; 32: 22. Wilson S. and Nutt D. Prescriber 2005; 19: 29-41 Wolkove N, et al. CMAJ 2007; 176: 1449-54

Cognitive and behavioral treatments for sleep difficulties aim to improve sleep by changing poor sleep habits and challenging negative thoughts attitudes and beliefs about sleep. (Montgomery P. et al., 2003). Several cognitive-behavioral interventions exist encompassing a broad range of treatments, from basic educational information to actual behavioral strategies. Table 7 lists various types of cognitive behavioral therapy interventions. It is very likely that combining several interventions may be required to produce and sustain positive outcomes.

Table 7: Other types of Cognitive Behavioral Therapy* [click here to return to algorithm]

Intervention	Principle(s)	Rationale(s)	Potential Candidates	Process	Comments
Stimulus Control	Helps the patient associate rapid sleep onset with the bed and bedroom.	Disrupt sleep-incompatible activities by training the individual to re-associate the bed, bedtime and bedtime stimuli with sleep rather than with the frustration or anxiety resulting from lying in bed trying to sleep.	Patients that associate bedroom with other activities besides sleeping (reading, watching TV etc.). Patients will need to be highly motivated and compliant.	Explain to the patient the rationale of each principle (see below) so the significance of each component of the overall treatment is understood. Instruct the patient on each item. Subsequent sessions are used to encourage the patient to comply with the instructions and to address any new concerns or difficulties. 1. Go to bed only when you feel tired; 2. Use the bed only for sleeping and sex. Do not read books, magazines, watch TV, or eat while in bed; 3. Leave the bed/room if you have not fallen to sleep within 15-20 minutes, leave the bedroom and engage in a relaxing activity, such as reading or listening to soothing music. Patients should not do activities that will stimulate them or reward them for being awake in the middle of the night, such as eating or watching television. Return to the bedroom only when feeling sleepy again. Repeat as often as necessary through the night; 4. Get up at the same time each morning regardless of the amount of sleep achieved in the previous night. (use an alarm clock if necessary); 5. Don't sleep during the day. Avoid napping 6. Correct environmental factors affecting sleep (pets or snoring bed partner); bedroom temperature; alcohol usage; watching the clock.	For sleep onset and sleep maintenance insomnia. Effective for primary, chronic insomnia, and co-morbid insomnia. Sleep onset latency and wake after sleep onset are reduced. Total amount sleep is increased. Additional improvements can be seen when combined with other interventions. The patient can be instructed on this intervention by general practitioner or other trained health care professionals.
Relaxation Therapy	Teach patients how to recognize and dissipate stress and tension.	Reducing level of stress and tension will improve sleep difficulties.	Patients who develop a high level of somatic arousal at night.	Relaxation therapy may be implemented before each sleep period. Two components have been suggested. 1. Physical component: Progressive muscle relaxation: Instruct the patient to tense and relax groups of muscles, first separately, then with the aim of relaxing the whole body at once. Begin with the muscles in the face, the muscles are contracted gently for 1-2 seconds and then relaxed. This is repeated several times. The same technique is used for other muscle groups, usually in the following sequence: jaw and neck, upper arms, lower arms, fingers, chest, abdomen, buttocks, thighs, calves, and feet. This cycle is repeated for approximately 45 minutes, if necessary. Biofeedback can also be included. 2. Mental component: Relaxation response: This begins by lying or sitting comfortably. The eyes are closed and relaxation is allowed to spread throughout the body. A relaxed, abdominal breathing pattern is established. Thoughts are redirected away from everyday thoughts and toward a neutral mental focusing device, such as a peaceful word or image~~. Imagery training, mediation, and/or hypnosis can also be added.~~ Relaxation therapy is sometimes combined with biofeedback to reduce somatic arousal.	Implementation requires minimal provider's time compared to other interventions. Most relaxation therapy can be administered by the patient through listening treatment verbatim or music/sounds on tape. Not all relaxation therapy is well supported in the literature.
Cognitive Behavioral Therapy	Assist patients to identify and challenge them to change or eliminate faulty beliefs and attitudes about sleep.	Identifying, challenging and changing a set of dysfunctional belief and attitudes about sleep and how it impacts day-to-day life.	Patients with dysfunctional beliefs and emotional distress that results in sleep disturbances. Examples: "I have to have 10 hours of sleep in order to function" and "if I try harder I will eventually fall asleep." Patients have often been diagnosed with psychophysiology insomnia and their polysomnographys are normal.	CBT is a strategy that combines several of the other interventions (e.g., stimulus control, sleep restriction) with or without relaxation therapy over several weeks. Therapists must explain the purpose of cognitive therapy to the patient. Faulty beliefs are identified using tools related to beliefs about sleep. Maladaptive beliefs and attitudes are replaced. Education to change faulty beliefs and attitudes about sleep should take place (e.g. provision the patient with a fact sheet listing what is normal and abnormal sleep) Reappraisal and attention shifting are involved.	Intervention is probably more important for older insomniacs. It is highly recommended for use in situations where medications are contraindicated or may be more likely to produce side effects. This intervention usually requires significant professional involvement. It is possible that cognitive therapy may need to be multi-component therapy for best outcomes. Patients are encouraged to complete sleep logs as they learn and apply various strategies. It provides patients with tools to apply in future. Disadvantage of CBT include the duration of therapy and the relatively few clinicians who are skilled at all of its components.
Sleep-Restriction	It is believed that excessive time in bed	Limit the time spent in bed at night and restrict	Patients with fragmented (frequent arousal) sleep patterns or difficulty falling	Progressive lengthening of sleep time after first improving sleep efficiency. 1. Determine the required average estimated amount of total sleep based on patient's diary for the previous 2 weeks.	Sleep restriction requires less time to implement than other non-pharmacological insomnia treatments. There is a tendency for the treatment

Therapy	causes fragmented sleep which then contributes in perpetuating insomnia. So, restricting time in bed can create a mild sleep deprivation and provide a more solid sleep.	sleep during the day thereby increasing the homeostatic drive for sleep The time spent in bed is limited to the actual time sleeping.	asleep. Older people, many of whom may have tried to compensate their poor sleep by spending more time in bed. Patients that wake up frequently or have difficulty falling asleep.	2. Restrict the time in bed to the average estimated total sleep time. Example: If a patient is in bed for 8 hours but only actually sleeps 6 of them, their allowed time in bed would be six hours. 3. Each week, determine the weekly sleep efficiency from the patient's sleep diary (total sleep/time in bed x 100). 4. When sleep efficiency exceeds 90%, increase the time allowed in bed by 15-20 minutes. Decrease it by 15-20 minutes when sleep efficiency is below 80%. 5. Adjust the total time in bed weekly until the expected optimal amount of sleep time is reached (i.e. sleep efficiency is between 80-90%). 6. Do not reduce time in bed to below 5 hours. 7. Brief midday naps are permissible, especially in the early phase of treatment. 8. When applying this to the elderly, some recommend reducing the time in bed only when sleep efficiency is below 75%.	results to be long term and there is a potential for excessive day-time sleepiness in older people undertaking this therapy. However, this type of treatment is thought to be effective in older people, many whom have tried to compensate for poor sleep by spending more time in bed.

Impaired motor and or cognitive performance attributable to the accumulation of benzodiazepines and their active metabolites following several days of repeated use at their recommended doses is a concern in certain vulnerable patients. Benzodiazepines (see Table 8) should be administered with caution in patient exhibiting signs or symptoms of depression. The least amount of drug that is feasible should be prescribed for the patients any one time. Withdrawal symptoms are more commonly noted after the discontinuation of higher than therapeutic doses of benzodiazepines. Gradual withdrawal is the preferred course for any patient taking benzodiazepines for a prolonged period. Patients with a history of seizures, regardless of their concomitant antiseizure drug therapy, should not be withdrawn abruptly from benzodiazepines. Individuals with a history of addiction to or abuse of drugs or alcohol should be under careful surveillance when receiving benzodiazepines because of the risk of habituation and dependence to such patients. Benzodiazepines should be given caution if given concomitantly with other drugs acting on the central nervous system.

Table 8: Comparison of Select Oral VA Benzodiazepine Formulary Agents (graded area) to other Non-VA Formulary Oral Benzodiazepine Agents More Commonly Prescribed to Treat Insomnia in U.S. **[Click here to return to algorithm]**

Agents	Time until Onset of Action, (min)	Peak Time, (h)	Elimination T 1/2 (range, h)	Protein Binding (%)	Metabolism/ Active Metabolites	Comments
Short-Acting (half-life < 10 h)						
oxazepam†	30-60[a]	2-4[b,e]	5.7-10[b,f] 2.8-5.7[a] 5-20 [b,d]	80[d] -87[b]	CYP450 (substrate unknown)/No	• 15mg capsule contains FD&C Yellow 5 (tartrazine) which may cause allergic-type reaction in certain susceptible individuals. • Caution in patients in whom a drop in blood pressure might lead to cardiac complications. • Increase in elimination half-life in the very elderly (>80 years of age) compared to younger subjects has been reported, due to a 30% increase in volume of distribution, as well as a 50% reduction in unbound clearance.
temazepam *	45-60[a]	1.2[e]-1.6[b]	3-25[a] 3.5-18.4[b]	96[2]	Not subjective to metabolic inhibition by CYP enzyme inhibitors or inducers/No	• Indicated for the short-term treatment of insomnia (generally 7-10 days). For patients in whom the drug is used for more than 2 to 3 weeks, periodic reevaluation is recommended to determine whether there is a continuing need.[b] • Dose should be individualized. For adults: Give 15-30mg before bedtime; 7.5mg may be sufficient for some. For elderly or debilitated patients: Initiate with 7.5mg-15mg until individual response is determined. • The usual precaution should be observed in patients with impaired renal or hepatic function. Use caution in severely depressed patients or those in whom there is any evidence of latent depression
triazolam*	15-30[a]	1.3[e] 1-2[b] 2-3[c]	1.5-5 [g,h]	89[g] 78-89 [d,b]	CYP3A4/No	• Indicated for the short-term treatment of insomnia (generally 7-10days). Use for more than 2-3 weeks requires complete reevaluation of the patients. • Use caution in elderly patients and patients with renal or hepatic impairment, depression or suicidal tendencies, drug abuse and dependence, chronic pulmonary insufficiency or apnea, seizure disorder.
Intermediate-acting (half-life 10-20 h)						
alprazolam†	N/A	1-2[b,d]	6.3-26.9[b] 12-15[d]	70[a]-80[b,d]	CYP3A4 and 3A5a/ Yes (although not sufficiently high concentrations to be of clinical importance) [g]	• Contraindicated in patients with acute narrow angle glaucoma. • Abrupt discontinuation should be avoided. Dosage should be limited to the smallest effective dose in the elderly or debilitated patients. • An increased plasma half-life has been observed in both alcoholic liver disease patients and obese patients. • Concentrations may be reduced by up to 50% in smokers compared to non-smokers
estazolam*	15-30[a]	2[b] – 3[e]	8-24 [a] 8-28 [b]	93[b]	CYP3A4 /Yes (although no significant contribution to the hypnotic effect is noted)[g]	• Indicated for the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. • Recommended initial dose for adults is 1 mg at bedtime. In small or debilitated older patients, a starting dose of 0.5mg-1mg[b] should be considered. • Closely related in structure to alprazolam and triazolam
lorazepam†	30-60[a]	2[e]-4[b,d]	10-20[b,d]	85 [b,d]	CYP450 (substrate unknown)/No	• Not recommended for use in patients with a primary depressive disorder or psychosis. • Observe the usual precaution for treating patients with impaired renal or hepatic function. Used in caution in patients with compromised respiratory function (e.g. COPD, sleep apnea syndrome)
Long-acting (half-life >20 h)						
quazepam*	20-45[a]	2[b] 2.5[e]	36[g] 39[b]	95[b]	CYP3A4 and CYP2C9/ Yes	• Selectively binds to BZ1 receptor • Indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, or early morning awakenings. • Initiate therapy at 15mg until individual responses are determined. In some patients, the dose may then be reduced to 7.5mg. Initiate therapy in geriatric patients at 7.5mg; if not effective after 1 to 2 nights, dosage may be increased to 15mg.

Prepared November 2007, Updated March 2013. Contact person: Janet H. Dailey, PharmD, VA Pharmacy Benefits Management Services.

† off-label use; *FDA-approved as sedative hypnotics; CYP450 = Cytochrome P450; NA = Not available. a. N Engl J Med 1997; 336:341-46. b. Facts and Comparison 4.0; 2007. [Accessed October 24, 2007]. c. Drug Intell Clin Pharm 1982; 16:650-6. d. J Clin Pharmacol 1994; 34:801-811. e. J Clin Psychiatry 2005; 66 Suppl 9: 31-41.f. Available at www.rxlist.com/cgi/generic/oxazepam_cp.htm (Accessed October 24, 2007). g. Psychopharmacology Bulletin 2003; 37:10-29.

Table 9: Comparison of VA Formulary Agent Zolpidem (graded area) to other Non-VA Formulary Newer Sedative-Hypnotic Agents **[Click here to return to algorithm]**

	Zolpidem IR (Ambien)	Zolpidem ER (Ambien CR)	Zolpidem SL (Edluar)	Zolpidem SL (Intermezzo)	Zaleplon (Sonata)	Eszopiclone (Lunesta)	Ramelteon* (Rozerem)
Strengths	5, 10 mg	6.25, 12.5 mg	5, 10 mg	1.75, 3.5 mg	5, 10 mg	1, 2, 3 mg	8 mg
Initial Dose (non-elderly)	Women: 5 mg Men: 5-10mg immediately before bedtime	Women: 6.25mg Men: 6.25-12.5 mg immediately before bedtime; do not crush, divide, or chew	Women: 5 mg Men: 5-10mg placed under the tongue once daily immediately before bedtime and only when able to stay in bed a full night (7-8 hours) before being active again.	3.5 mg for adult men and 1.75 mg for adult women when patient wakes in the middle of the night (MOTN); only take if patient has at least 4 hours of bedtime remaining before the planned time of waking	10 mg immediately before bedtime OR after patient has had difficulty falling asleep	2 mg immediately before bedtime; must be able to get 8 or more hours of sleep	8 mg within 30 minutes of bedtime
Maximum Dose	10 mg	12.5 mg	10mg placed under the tongue	3.5 mg for men and 1.75 mg for women placed under the tongue times once if MOTN awaking is followed by difficulty returning to sleep	May titrate to max of 20 mg if no benefit from lower dose	Can titrate to max dose of 3 mg	8 mg
Food Considerations	For faster onset, do not give with or immediately after a meal	For faster onset do not give with or immediately after a meal.	Do not administer with or immediately after a meal; should not be swallowed nor taken with water	Do not administer with or immediately after a meal; should not be swallowed nor taken with water	Effects may be reduced if taken with or immediately after a heavy/high-fat meal	Effects on sleep latency may be reduced if taken immediately after/with a heavy/high-fat meal	Do not take with or immediately after a high-fat meal
Dose adjustments in special populations	Elderly, debilitated or patients with hepatic impairment should start with 5 mg, may titrate to 10 mg	Elderly, debilitated or patients with hepatic impairment should start with 6.25 mg, may titrate to 12.5 mg	Elderly, debilitated or patients with hepatic impairment should start with 5 mg daily. The total daily dose should not exceed 10 mg	1.75 mg for elderly, hepatic impairment, and patients taking concomitant CNS depressants.	Reduce dose to 5 mg in mild to moderate hepatic impairment, do not use in severe hepatic impairment. Start elderly / debilitated patients at 5 mg; doses > 10 mg not recommended; start at 5 mg when given with cimetidine	1 mg starting dose in severe hepatic impairment. In patients taking potent CYP3A4 inhibitors, start with 1 mg; do not exceed 2 mg.	No dose adjustment for elderly; do not use in severe hepatic impairment; use with caution in moderate hepatic impairment

* hypnotic only. DoD Drug Class Review - Newer Sedative Hypnotics. Prepared by DoD Pharmacoeconomic Center for the Feb 07 meeting of the DoD Pharmacy & Therapeutics Committee. Zolpidem Tartrate Sublingual Tablets Abbreviated Drug Review. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacists Executives, Veterans Health Administration, Department of Veterans Affairs; May 2012.

Table 10: Pharmacokinetics of VA Formulary Agent Zolpidem IR (graded area) to other Non-VA Formulary Newer Sedative-Hypnotic Agents
[Click here to return to algorithm]

Drug	Estimated half-life (hr)*	Tmax (hr)	Plasma protein binding	Bioavailability	Metabolism / Elimination	Comments

Prepared November 2007, Updated March 2013. Contact person: Janet H. Dailey, PharmD, VA Pharmacy Benefits Management Services.

Zolpidem IR	2.5	1.6	92.5%	70%	Primarily renal excretion	No active metabolites. Olubudon et al (2003)† reported substantial decreases in clearance in the elderly, particularly elderly men; possible relation to levels of free testosterone, which is known to affect the CYP450 system
Zolpidem ER	2.8	1.5	92.5%		Primarily renal excretion	No active metabolites
Zolpidem SL (Edluar)	2.85 (5mg) 2.65 (10mg)	1.37	92.5%		Primarily renal excretion	No active metabolites
Zolpidem SL (Intermezzo)	2.5 (3.5mg)	0,58-1.25	93%		Primarily renal excretion	No active metabolites
Zaleplon	1	1	~60%	30% (due to rapid first pass metabolism)	Primarily metabolized by aldehyde oxidase, to a lesser extent by P450 3A4; mostly renal excretion (71%) as metabolites; 17% in feces as metabolite	Significant first pass hepatic metabolism; no active metabolites.
Eszopiclone	6 (non-elderly); 9 (elderly	1	52-59%	80%	Hepatic metabolism (P450 3A4 and 2E1); primarily renal excretion as metabolites	No active metabolites; does not appear to interconvert to (R) zopiclone; AUC increases by 41% in elderly (≥ 65 years)
Ramelteon*	1 - 2.6 (M-II metabolite 2-5)	45 min	82%, mostly to albumin	1.8% (due to rapid first pass metabolism)	Metabolism primarily via oxidation; major hepatic isoenzyme 1A2, also 2C, 3A4; primarily renal excretion; the major metabolite (M-II) is rapidly produced, with a systemic exposure 20-40-fold higher than parent drug.	Significant first pass metabolism; high intersubject variability; major metabolite (M-II) is active but has substantially less affinity for MT_1 and MT_2; M-II has weak affinity for serotonin 5-HT_{2B}, but no other receptor types.

* hypnotic only. DoD Drug Class Review - Newer Sedative Hypnotics. Prepared by DoD Pharmacoeconomic Center for the Feb 07 meeting of the DoD Pharmacy & Therapeutics Committee.

† Olubudon JO, Ochs HR, von Moltke LL, et al. Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men. Br J Clin Pharmacol 2003; 56:297-304. .

Zolpidem Tartrate Sublingual Tablets Abbreviated Drug Review. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacists Executives, Veterans Health Administration, Department of Veterans Affairs; May 2012.

Table 11: Special Considerations for the Use of Newer Sedative Hypnotic Agents [Click here to return to algorithm]

	Zolpidem IR† (Ambien)	Zolpidem ER (Ambien CR)	Zoplidem SL (Edluar)	Zopidem SL (Intermezzo)	Zaleplon (Sonata)	Eszopiclone (Lunesta)	Ramelteon* (Rozerem)
Contraindications	None known	Hypersensitivity	Hypersensitivity to oral zolpidem	Hypersensitivity to oral zolpidem	Hypersensitivity	None known	Hypersensitivity
Pediatric patients	Safety & efficacy not established	Safety & efficacy not established	Safety & efficacy not established	Safety & efficacy not established	Safety & efficacy not established	Safety & efficacy not established	Not studied; associated with decreases in testosterone levels and increases in prolactin levels in adults; effect on reproductive axis in children & adolescents unknown
Elderly patients	Cmax, half-life, total exposure significantly increased; reduce dose. Reports of falls, confusion among patients ≥ 70 years, primarily with doses	Data limited; reduce dose	Elderly or debilitated patients may be especially sensitive to the effect of zolpidem. The recommended dose in these patient populations is 5 mg	Recommended dose in women and men over 65 years old is 1.75mg take only once per night if needed.	PK similar to non-elderly, reduce dose because appear more sensitive to effects; adverse effects similar to placebo in short-term trials (14 nights)	Total exposure increased & half-life prolonged in elderly, adjust dose; pattern of adverse effects in 2-week studies at 2-mg dose not different from	Total exposure and Cmax higher in elderly patients; no dose adjustment recommended; no overall differences in safety or efficacy noted

	Zolpidem IR† (Ambien)	Zolpidem ER (Ambien CR)	Zoplidem SL (Edluar)	Zopidem SL (Intermezzo)	Zaleplon (Sonata)	Eszopiclone (Lunesta)	Ramelteon* (Rozerem)
	>10 mg		once daily immediately before bedtime.			non-elderly pts	in clinical trials
Race / gender	No differences noted based on race. Lower dose should be prescribed for women.	No differences noted based on race. Lower dose should be prescribed for women.	No differences noted based on race. Lower dose should be prescribed for women.	No difference noted based on race. Lower dose is recommended for women and men over 65 years of age.	Cmax and AUC increased in Asian populations	No differences noted based on race or gender	No gender differences noted
Pregnancy & Lactation	Pregnancy Category C; small amounts in breast milk; inhibited breast milk production in rat study; not recommended while breastfeeding.	Pregnancy Category C; small amounts in breast milk; inhibited breast milk production in rat study; not recommended while breastfeeding.	Pregnancy Category C; small amount in breast milk.	Pregnancy Category C	Pregnancy Category C; small amounts in breast milk (unlikely to be clinically important [Darwish 1999[126]]); not recommended while breastfeeding	Pregnancy Category C; not known if excreted in breast milk; not recommended while breastfeeding	Pregnancy Category C; not known if excreted in breast milk; not recommended while breastfeeding
Renal impairment	PK not altered; no dose adjustment.	ER formulation not studied; should be similar to IR.	No dosage adjustment.	No dosage adjustment.	PK not altered; no dose adjustment; not studied in severe renal impairment	PK not altered in mild, mod, severe renal impairment; no dose adjustment needed	PK not altered; no dose adjustment needed even in dialysis patients
Hepatic impairment	Cmax 2-fold higher; total exposure 5-fold higher in hepatic impairment; mean half-life of 9.9 hours in cirrhotic pts; adjust dose	ER formulation not studied; should be similar to IR	Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects.	The recommended dose in patients with hepatic impairment is 1.75mg, taken only once per night if needed.	Clearance reduced in compensated & non-compensated cirrhotic pts; reduce dose in mild to moderate hepatic impairment; do not use in severe	Use with caution; total exposure doubled in severe hepatic impairment; reduce dose; no dose adjustment in mild to moderate	Exposure increased almost 4-fold with mild hepatic impairment; more with moderate. Use with caution in moderate hepatic impairment; do not use in severe
Psychiatric patients	Use with caution in depressed patients, intentional overdose more common	Use with caution in depressed patients, intentional overdose more common	Dosage adjustment may be necessary when combined with other CNS-depressant drugs because of the potentially additive effects. Use with caution to patients exhibiting signs or symptoms of depression.	Dosage adjustment may be necessary when combined with other CNS-depressant drugs because of the potentially additive effects. Use with caution to patients exhibiting signs or symptoms of depression.	Use with caution in depressed patients, intentional overdose more common	Use with caution in depressed patients, intentional overdose more common	
Other	No respiratory depressant effects in with mild to moderate COPD; however, reduction in Total Arousal Index and oxygen saturation in patients with mild to moderate sleep apnea; precautions with compromised	Data in patients with comorbid illnesses is limited; precautions similar to IR.	Sedative-hypnotics have the capacity to depress respiratory drive; precautions should be taken if zolpidem is prescribed to patients with compromised respiratory function.	Sedative-hypnotics have the capacity to depress respiratory drive; precautions should be taken if zolpidem is prescribed to patients with compromised respiratory function.	Contains FD&C Yellow No 5 (tartrazine), which is rarely associated with allergic type reactions (more common in patients who also have aspirin hypersensitivity)		1-night trial in COPD patients showed no respiratory depressant effect; 1-night trial in sleep apnea showed no exacerbation in mild to moderate sleep apnea. Not studied and therefore not recommended in severe sleep apnea or severe COPD

	Zolpidem IR† (Ambien)	Zolpidem ER (Ambien CR)	Zoplidem SL (Edluar)	Zopidem SL (Intermezzo)	Zaleplon (Sonata)	Eszopiclone (Lunesta)	Ramelteon* (Rozerem)
	respiratory function; post-marketing reports of respiratory insufficiency.						

†zolpidem-only agent listed on this table that resides on VA National Formulary * hypnotic only. DoD Drug Class Review - Newer Sedative Hypnotics. Prepared by DoD Pharmacoeconomic Center for the Feb 07 meeting of the DoD Pharmacy & Therapeutics Committee. . Zolpidem Tartrate Sublingual Tablets Abbreviated Drug Review. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacists Executives, Veterans Health Administration, Department of Veterans Affairs; May 2012.

Table 12: Drug Interactions of Newer Sedative Hypnotic* Agents (primarily based on labeling)

[Click here to return to algorithm]

Drug Causing Effect	Drug Affected		Description
Ketoconazole (& other potent 3A4 inhibitors: itraconazole, clarithromycin, troleandomycin, nefazodone, ritonavir, nelfinavir)	Eszopiclone, zaleplon, ramelteon, zolpidem	↑	*Eszopiclone* - Ketoconazole, a potent 3A4 inhibitor, increased systemic bioavailability of eszopiclone by 2.2 fold *Zaleplon* - Erythromycin, a potent 3A4 inhibitor, increased maximum concentrations of zaleplon by 34%, AUC by 20%; 3A4 is a minor pathway for zaleplon metabolism; routine dose adjustment not considered necessary *Ramelteon* – Ketoconazole increased total exposure of ramelteon by 84% and Cmax by 36%; use with caution *Zolpidem* – Itraconazole increased total exposure of zolpidem by 34%; no effect on drowsiness, postural sway, psychomotor performance
Rifampin (& other potent 3A4 and general CYP P450 inducers: phenytoin, carbamazepine, phenobarbital)	Eszopiclone, zaleplon, ramelteon, zolpidem	↓	*Eszopiclone* - Rifampicin, a potent inducer of CYP450 3A4, decreased exposure to racemic zopiclone by 80%; may also occur with eszopiclone *Zaleplon* - Rifampin decreased exposure to zaleplon by about 80%; however, 3A4 is a minor pathway for zaleplon metabolism *Ramelteon* – Rifampin decreased total exposure to ramelteon by about 80% after a 32 mg dose Zolpidem – Rifampin decreased total exposure 73%, Cmax 58%, half-life (36%) and decreased pharmacodynamic effects
Alcohol	Eszopiclone, zaleplon, ramelteon, zolpidem		No PK interaction; additive but not synergistic effect on psychomotor performance
Olanzapine	Eszopiclone		Impairment of psychomotor performance upon coadministration
Thioridazine	Zaleplon		Impairment of psychomotor performance upon coadministration[a]
Promethazine	Zaleplon	↓	Decreased maximum concentrations of zaleplon by 15%; no information on pharmacodynamic effects, use caution
Drugs inhibiting aldehyde oxidase (diphenhydramine)	Zaleplon		No PK interaction after single dose; pharmacodynamic effect possible
Drugs inhibiting aldehyde oxidase and 3A4 (cimetidine)	Zaleplon	↑	Inhibits both metabolic pathways, increases mean concentrations by about 85%, reduce initial dose
Drugs inhibiting 1A2 (fluvoxamine)	Ramelteon	↑	Fluvoxamine 100 mg BID for 3 days prior to a single 16 mg dose of ramelteon increased AUC by 190-fold and Cmax by 70-fold. Do not give with fluvoxamine.
1A2 inducers (e.g., smoking)	Ramelteon	↓	Smoking induces 1A2 and may decrease efficacy of ramelteon
Imipramine	Zolpidem		Decreased alertness
Chlorpromazine	Zolpidem		Decreased alertness and psychomotor performance
Sertraline	Zolpidem	↑	Increased zolpidem Cmax by 43% and decreased Tmax by 53%[b]

Ramelteon-hypnotic only. DoD Drug Class Review - Newer Sedative Hypnotics. Prepared by DoD Pharmacoeconomic Center for the Feb 07 meeting of the DoD Pharmacy & Therapeutics Committee.

[a]Hetta J, Broman JE, Darwich M, et al. Psychomotor effects of zaleplon and thioridazine coadministration. Eur J Clin Pharmacol 2000; 56:211-17.

[b]Allard S, Sainati SM, Roth-Schechter BF. Coadministration of short-term zolpidem with sertraline in healthy women. J Clin Pharmacol 1999; 39:184-191.

Recommendation for Use: Zolpidem Immediate Release (IR)
VHA Pharmacy Benefits Management Service and Medical Advisory Panel

The following recommendations are based on current medical evidence. The content of the document is dynamic and will be revised as new clinical data become available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

EXCLUSION RECOMMENDATIONS

- Patients with alcohol abuse or dependence or active use of illicit drugs
- No attempts or consideration has been made and documented of contributing co-morbid conditions or medications known to interfere with sleep.

INCLUSION RECOMMENDATIONS

For Short-Term Therapy for Insomnia

- Patient with acute (short-term) insomnia defined as periods of sleep difficulty lasting less than one month and basic sleep interventions (e.g., sleep hygiene, relaxation training) have failed to improve sleep difficulties
- Patient with acute (short-term) insomnia until treatment associated with any underlying psychiatric and/or medical illnesses takes effect (e.g., depression)

For Long-Term Therapy for Insomnia

- Patient with DSM-IV criteria for chronic primary insomnia (≤ 6.5 hours of sleep/night and requires > 30 min to fall asleep each night for at least 1 month) **AND** basic sleep interventions (e.g., sleep hygiene, relaxation training) failed to improve sleep difficulties.
  Note: Treatment such as cognitive behavioral therapy (e.g., stimulus control, sleep restriction, cognitive therapy, and sleep education), IF AVAILABLE and FEASIBLE, must be considered prior to or in combination with zolpidem IR.
- Patient with chronic insomnia associated with comorbid medical or psychiatric conditions that exacerbate or contribute to both the nighttime complaints and or daytime impairment that has lasted for more than three weeks and is persistent without treatment AND basic sleep interventions (e.g., sleep hygiene, relaxation training) failed to improve sleep difficulties.
  Note: Treatment such as cognitive behavioral therapy (e.g., stimulus control, sleep restriction, cognitive therapy, and sleep education), IF AVAILABLE and FEASIBLE, must be considered prior to or in combination with zolpidem IR.

Dosage and Administration

For Short-Term Therapy for Insomnia

- Short trial of Zolpidem IR; Women 5mg; Men 5-10mg orally immediately before bedtime x 7-10 days with no refills.

For Long-Term Therapy for Insomnia

- Zolpidem IR: Women 5mg; Men 5-10 mg orally immediately before bedtime x 2 refills.
  - For both men and women, the 5 mg dose could be increased to 10mg if needed, but the higher dose is more likely to impair next-morning driving and other activities that require full alertness.
  - For selected patients, consider minimizing the frequency e.g., take no fewer than 3 and no more than 5 tablets per week (3-5x/week - QTY 20/month x 2 refills)
- Dual use of zolpidem with other formulations of zolpidem is not recommended. Zolpidem used concurrently with other sedative hypnotics or other medications used to treat insomnia is not recommended.

Recommended Monitoring

- It is strongly recommended that patients be evaluated within 2-3 weeks of the initial Rx to document any improvement in the symptoms related to insomnia. Patients should be re-evaluated regularly and adjunctive behavioral modification therapy be continued. If not done, reconsideration should be made whether Rx for zolpidem IR should be continued.
- The failure of symptoms of insomnia to improve after 7-10 days of treatment for short-term therapy may indicate the presence of an underlying condition that needs to be evaluated.
- Consultation with a sleep disorder specialist (e.g., neurologists, pulmonologists, psychiatrists, medical practitioners board certified in sleep medicine) or a behavioral therapist that are experienced in sleep intervention techniques is recommended if the standard behavioral treatments are not effective and patient is not a candidate for pharmacologic treatment or pharmacologic agent is not continued.

Issues For Consideration

- The evaluation of insomnia should include assessment of other drugs or conditions (e.g. chemical dependence, sleep apnea) that may be interfering with sleep. There are no studies showing benefit in the combination of benzodiazepines and zolpidem IR in the treatment of insomnia.
- Prior to using medications to treat insomnia, clinicians should ask the patient about use of caffeine and other stimulants which can exacerbate insomnia; these include over the counter products (e.g., ephedrine or pseudoephedrine) and beverages such as coffee (drip or brew), tea, ice tea and various sodas (e.g., colas, citrus drinks) and sports/energy drinks (e.g., super-caffeinated drinks)
- An adequate sleep history should be obtained. Provide patient with a sleep diary with instructions. Document the type of insomnia disorder at each visit. Instruct patient on the basic sleep-hygiene interventions.
- Inform patients about any risks of taking zolpidem IR and the prescribed duration of therapy.
- No studies are available using zolpidem IR in combination with benzodiazepines for the treatment of insomnia.
- If the patients' activities the day after the use of zolpidem IR (or any other sedative hypnotic) require optimal alertness or involves skilled work and where impairment of performance could be a danger to themselves or others, zolpidem should be avoided. Advise patients not to drive when they feel sleepy, dizzy or are experiencing a lack of concentration. However, it should also be made clear to them that the absence of such feelings does not mean their performance is normal.
- Residual effects depend on the dose administered; start with the lowest dose possible, particularly in the elderly. Do not double the dose without consideration of the consequences of residual effects. For patients whom are still working or active, consider initiating therapy on a weekend or before a day off. Use of hypnotics in combination with other psychoactive drugs largely increases the risk of residual effects; use of multiple drugs should be avoided.
- There are no adequate and well-controlled studies in pregnant women. Zolpidem IR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Use of zolpidem in nursing mothers is not recommended.
- ***Patient Resources for Basic Hygiene Education:*** ***http://www.womenshealth.gov/faq/insomnia.htm#5;*** ***http://www.aasmnet.org/FactSheet.aspx*** ***and*** ***http://www.sleepfoundation.org/***
- ***Example of a sleep diary:*** ***http://www.nhlbi.nih.gov/health/prof/sleep/insom_pc.pdf***
- ***Professional Education:*** ***http://www.sleepfoundation.org/*** ***and*** ***http://www.ahrq.gov/clinic/epcsums/insomnsum.htm***

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